REMARKS / ARGUMENTS

In response to the Examiner's communication, applicant has amended the title to more clearly indicate the invention to which the claims are directed, as requested by the Examiner.

In addition, applicant has amended the abstract to provide a concise statement of the technical content of the application, as requested by the Examiner.

The applicant has also made some minor changes to the specification to correct typographical and other errors due to inadvertence.

Concerning the drawings, applicant resubmits Figures 5A and 5B showing where the reference numbers are pointing – applicant would like to advise the Examiner that formal drawings are being prepared and that these will be forwarded to the Examiner shortly.

Applicant submits that none of the above changes add new subject matter to this application.

Claim 1 has been amended to remove the term MS^3, as objected to by the Examiner under 35 U.S.C. 112, second paragraph. Applicant submits that this amendment does not limit the claim in any way. Moreover, applicant would like to advise the Examiner that the term MS^3 would be known to those in the art as meaning mass selection steps followed by two fragmentation steps leading to one or more mass spectra (see page 11, lines 1 to 3 of the specification).

The Examiner has objected to claims 14 and 16–19 as being anticipated by Thomson et al. Applicant is well aware of the Thomson et al. Invention. Indeed one of the inventors in the present case is listed as an inventor in the Thomson et al. application. Applicant advices the Examiner that the Thomson et al. reference does not teach the use of resonant excitation. The only excitation described in Thomson et al. is in the axial direction only (see col. 13, line 54 of that reference) with no resonance.

Moreover, the Thomson et al. reference specifically states that there is no need to operate at the resonant frequency in order to obtain the desired results described in that reference (see col. 13, line 66). In fact, in Thomson et al., an objective is to oscillate all of the ions axially so that all of the ions are fragmented in a non-mass-selective fashion. Accordingly, applicant submits that there can be even no suggestion of modifying Thomson et al. to excite the ions at a resonant frequency in order to fragment just one m/z value as disclosed in the present invention.

Applicant submits that Thomson et al. does not disclose, nor even suggest, an apparatus, for analyzing a substance by resonance excitation of selected ions and selective collision-induced dissociation, where the apparatus comprises:

an ion source for generating a stream of ions;

a collision cell, including a quadrupole rod set, for receiving a stream of precursor ions and provided with a collision gas, for collision-induced dissociation between the parent ions and the buffer gas;

a power supply connected to the quadrupole rod set for generating an RF field in the quadrupole rod set for guiding ions and for applying an additional alternating current field at a frequency selected to excite a desired ion;

a modulation means connected to the power supply, for modulating the alternating current signal, whereby periods in which said alternating current signal are applied alternate with periods in which the alternating current signal is not applied.

Applicant submits that claims 15–19 are also allowable as they depend on claim 14.

The Examiner also objects to claims 1–9, 13, and 15 as being obvious in view of Thomson et al. Applicant advises the Examiner, however, that Thomson et al. does not teach modulating an AC signal in a multipole. Rather, Thomson et al. teaches modulating an axial DC field in order to fragment ions. Column 5, lines 6–12 of Thomson et al. merely describes a conventional RF/DC quadrupole used for mass resolution.

Applicant submits that the present invention excites only one m/z value by using resonant excitation. This ensures that only one m/z value is fragmented among all the m/z values present. Furthermore, the excitation voltage is turned on and off rapidly in order to produce a spectrum that represents the difference of the on/off condition, enabling the identification of the fragments of only the ion that is excited to fragment.

Applicant submits that the Thomson et al. reference does not disclose a method of analyzing a substance, wherein the method comprises:

(1) creating a stream of ions in said substance;

(2) supplying the stream of ions and a collision gas to a multipole and providing an RF signal to the multipole, whereby the multipole functions as a collision cell;

(3) fragmenting said ions in the RF multipole by collisions with the gas molecules, in order to form primary fragment ions;

(4) supplying additional alternating current to the multipole at a frequency selected to cause resonance excitation of a desired primary fragment ion mass-to-charge ratio, whereby ions with said desired primary fragment ion mass-to-charge ratio are excited and undergo collisions with the gas molecules causing production of secondary fragment ions;

(5) modulating the alternating current signal applied in step (4) whereby periods in which said alternating current signal is applied alternate with periods in which the alternating signal is not applied;

(6) detecting the ion signal after fragmentation with a mass spectrom ter and collecting one set of data for one spectrum, representative of the ion spectrum when the alternating current signal is applied and another set of data for another spectrum, representative of the ion spectrum when the alternating current signal is not applied; whereby said other spectrum can be subtracted from said one spectrum, to generate a subtracted spectrum showing the secondary fragment ions without the presence of the primary fragment ions except for any said primary fragment ions which are generated by step (4).

Applicant submits that claims 2–13, and new claim 20 are also allowable as they depend on claim 1.

Applicant submits that U.S. Patent 5,763,878, to which the Examiner does not rely, discloses the use of a multipole to trap ions and "outpulse" them all together into a time-of-flight mass spectrometer, and does not disclose any use of excitation voltages in a multipole or quadrupole in order to fragment ions.

Applicant submits that this is a complete response to the Examiner's action, and that favourable consideration be given to this application. Should the Examiner have anything further to discuss to bring this application into condition for allowance, applicant invites the Examiner to contact the undersigned by telephone at (416) 957-1697.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Applicant respectfully requests that a timely Notice of Allowance be issued in this case.

Respectfully submitt d,
Bereskin & Parr

By _____
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Title:

The Title has been amended as follows:

~~ANALYSIS TECHNIQUE, INCORPORATING SELECTIVELY INDUCED COLLISION DISSOCIATION AND SUBTRACTION OF SPECTRA~~ METHOD AND APPARATUS FOR ANALYZING A SUBSTANCE USING MS^n ANALYSIS

In the Abstract:

The Abstract has been amended as follows:

A method of and apparatus for analyzing a substance takes a stream of ions in said substance and supplies the ions to a collision cell including a quadrupole rod set for guiding the ions and a buffer gas. An RF voltage is applied to the quadrupole rod set to guide ions. An additional alternating current signal is applied to the quadrupole rod set at a frequency selected to cause resonance excitation of the secular frequency of a desired ion, whereby said desired ions are excited and undergo collision with the buffer gas causing fragmentation. The ~~invention then provides modulation of the~~ alternating current signal is then modulated, ~~applied~~ whereby periods in which said alternating current signal is applied alternate with periods in which said alternating signal is not applied. The ion spectrum after fragmentation is collected to generate one set of data for one spectrum, representative of the ion spectrum when the alternating current signal is applied, and ~~a~~ another set of data for another spectrum, representative of the ion spectrum when the alternating current signal is not applied. These two

spectra can then be subtracted ~~to give a spectrum indicative of the effect of fragmentation~~.

In the Specification:

The paragraph on page 6, line 10, has been amended as follows:

(2) supplying the stream of ions and a collision gas to a multipole and providing an RF signal to the multipole, whereby the ~~quadrupole~~ multipole functions as a collision cell;

The paragraph on page 7, beginning at line 10, has been amended as follows:

In one embodiment, the alternating current signal is at a frequency that excites the desired primary fragment ion.

The paragraph on page 14, beginning at line 16, has been amended as follows:

However, here, to replace the final quadrupole Q3 and ~~on~~ detector 20, there is provided a time-of-flight (TOF) mass analyzer 42. In known manner, the TOF analyzer of section 42 includes a gating region 44 and a detector 46. Thus, in use, ions pass into the gating region 44 and are gated or pulsed out to travel down the main body of the TOF 42, following a drift tube, until detected at a detector 46.

In the Claims:

Claim 1 has been amended as follows:

1. (Amended) A method of analyzing a substance, the method comprising~~consisting of~~:

(1) creating a stream of ions in said substance;

(2) supplying the stream of ions and a collision gas to a multipole and providing an RF signal to the multipole, whereby the ~~quadrupole~~ multipole functions as a collision cell;

(3) fragmenting said ions in the RF multipole by collisions with the gas molecules, in order to form primary fragment ions;

(4) supplying additional alternating current to the multipole at a frequency selected to cause resonance excitation of a desired primary fragment ion mass-to-charge ratio, whereby ions with said desired primary fragment ion mass-to-charge ratio are excited and undergo collisions with the gas molecules causing production of secondary fragment ions;

(5) modulating the alternating current signal applied in step (4) whereby periods in which said alternating current signal is applied alternate with periods in which the alternating signal is not applied;

(6) detecting the ion signal after fragmentation with a mass spectrometer and collecting one set of data for one spectrum, representative of the ion spectrum when the alternating current signal is applied and another set of data for another spectrum, representative of the ion spectrum when the alternating current signal is not applied;

whereby said other spectrum can be subtracted from said one spectrum, to generate a subtracted spectrum showing the secondary fragment ions without the presence of the primary fragment ions except for any said primary fragment ions which are generated by step (4)~~, whereby to obtain MS^3 information~~.

Claim 10 has been amended as follows:

10. (Amended) A method as claimed in any one of claims 1, 2, 3, 4, or ~~8 or 9~~, which includes subtracting said one spectrum from the other spectrum to obtain a subtracted spectrum.

Claim 14 has been amended as follows:

14 (Amended) An apparatus, for analyzing a substance by resonance excitation of selected ions and selective collision-induced dissociation, the apparatus comprising:

an ion source for generating a stream of ions;

a collision cell, including a quadrupole ~~ion guide~~ rod set, for receiving a stream of precursor ions and provided with a collision gas, for collision-induced dissociation between the parent ions and the buffer gas;

a power supply connected to the quadrupole rod set for generating an RF field in the quadrupole rod set for guiding ions and for applying an additional alternating current field at a frequency selected to excite a desired ion;

a modulation means connected to the power supply, for modulating the alternating current signal, whereby periods in which said alternating current signal are applied alternate with periods in which the alternating current signal is not applied.

Claim 15 has been amended as follows:

15. (Amended) An apparatus as claimed in claim ~~13~~14, which additionally includes a detector for detecting fragment ions exiting the collision cell, a switch connected to the detector, two data storage devices connected to the switch, and a connection between the modulation control unit and the switch, whereby the switch switches detected data for periods when the alternating current signal is applied to one data storage device and collected data for periods when the alternating current signal is not applied to the other storage device.